



## Endothelial dysfunction and oxidative stress

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The various forms of atherosclerosis, including coronary thrombosis, stroke and peripheral arterial disease, continues to be the leading cause of death worldwide. Black Africans are today too suffering from an increased incidence of cardiovascular disease due to the adoption of a western lifestyle and diet.

The endothelium (the largest organ in the body) controls vascular smooth muscle tone by secreting relaxing and contracting factors. There is a constant release of endothelium-derived relaxing factors (EDRFs), whose biologic activity is provided by nitric oxide (or similar molecules) and constantly counteracts vasoconstrictor substances such as noradrenaline, angiotensin II or endothelin I. The normal functioning endothelium is able to increase the release of EDRFs in response to physiological stimuli, such as the stress exerted by the circulating blood, or to humoral stimulation by vasoactive substances such as acetylcholine or bradykinin. The endothelium is in effect both a target and a modulator of blood pressure-related and hormonal influences.

Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function, control of volume and electrolyte content of the intravascular and extravascular spaces.

As we age, some of the specialized functions of the endothelium become blunted. The self renewal process weakens, the endothelial barrier becomes leaky and signals to the middle wall smooth muscle cells that regulate their function become altered. The vascular aging process and atherosclerosis become intertwined as we age.

### The arterial wall under attack (excerpt left October 2005)

High blood pressure, elevated LDL and triglycerides, cigarette smoking, diabetes, obesity, and lack of exercise contribute to endothelial dysfunction and the subsequent development of atherosclerosis.<sup>15-25</sup>

Additional endothelial-damaging factors include excess levels of glucose, insulin, iron, homocysteine, fibrinogen, and C-reactive protein, as well as low HDL and free testosterone (in men).<sup>3,9,10,24,26-28</sup>

Homocysteine is particularly dangerous because it can induce the initial injury to the endothelium. Homocysteine then facilitates oxidation of the fat/LDL that accumulates beneath the damaged endothelium, and finally contributes to the abnormal accumulation of blood components around the atherosclerotic lesion.<sup>29</sup>

Fibrinogen is a clotting factor that accumulates at the site of the

endothelial lesion. Fibrinogen may contribute to plaque buildup or participate in blood clot-induced blockage of an artery after an unstable atherosclerotic plaque ruptures.<sup>30</sup>

Glucose at even high-normal levels may accelerate the glycation process that causes arterial stiffening, while high-normal fasting insulin inflicts direct damage to the endothelium.<sup>31-36</sup>

High levels of iron promote LDL oxidation in the damaged endothelium, while low levels of testosterone appear to interfere with normal endothelial function.<sup>9,11,14</sup>

C-reactive protein is not only an inflammatory marker, but also directly damages the endothelium. Chronic inflammation, as evidenced by persistent high levels of C-reactive protein, creates initial injuries to the endothelium and also accelerates the progression of existing atherosclerotic lesions.<sup>3,27</sup>

In response to numerous published studies, health-conscious people are altering their diets, taking drugs, hormones, and dietary supplements, and trying to exercise regularly in order to reduce these atherosclerosis risk factors. However, these efforts alone cannot be completely successful because age itself is a major risk factor for atherosclerosis.

Atherosclerotic risk conferred by age is attributable in large measure to pathological endothelial dysfunction.<sup>37,38</sup> As noted earlier, endothelial



dysfunction is not synonymous with atherosclerosis, but the two processes are increasingly intertwined with advancing age.

## Endothelial dysfunction markers:

1. VEGF (Vascular endothelial growth factor)
2. ADMA (Asymmetric dimethyl-arginine)
3. VCAM-1 (vascular cell adhesion molecules)
4. NOS (Nitric oxide synthase)

ADMA is involved in the pathogenesis of hypertension and atherosclerosis through its inhibition of the formation of the endogenous vasculoprotective molecule, nitric oxide (NO). Determination of ADMA can thus help to predict both the likelihood of developing cardiovascular disease and its prognosis. A new competitive ELISA test for ADMA is a useful and fully validated tool suitable for routine laboratory use.

Available tests to detect endothelial dysfunction in South Africa include :

- a) Ultra sensitive CRP
- b) Von Willebrand Factor (WF)
- c) PAI-1 (Plasminogen activator inhibitor-1)
- d) FDP (Fibrinogen degradation products) - as D-dimer
- e) NT-proBNP
- f) Homocysteine
- g) Active renin
- h) Lipids (lipogram) and lipoproteins
- i) ACE (angiotensin converting enzyme)

An article published online on October 21, 2008 in the journal *Nutrition & Metabolism* reported the discovery of Italian researchers of an association between decreased plasma levels of several antioxidants and early carotid atherosclerotic lesions in asymptomatic middle-aged individuals.

“Atherosclerosis remains clinically

mute for a long time and frequently manifests itself with an acute cardiovascular event; therefore, the possibility of detecting the disease in a subclinical phase and reducing or reversing its progression is an issue of relevance,” the authors write. “Antioxidants, which may inhibit lipid peroxidation, could play an important protective role against the formation of simple and complex atherosclerotic lesions, which progressively protrude into the arterial lumen, causing stenosis or occlusion. In particular, increased carotid intima-media thickness represents an early phase of the atherosclerotic process and is widely used as a marker of subclinical atherosclerosis which correlates with established coronary heart disease.”

Two hundred and twenty men and women between the ages of 45 and 65 without history of transient ischemic attack, stroke, or other conditions related to carotid artery disease were enrolled at the San Camillo de Lellis Hospital, in Manfredonia, Italy. Participants underwent ultrasonographic evaluation of the extracranial carotid arteries, and blood samples were analysed for lipids, C-reactive protein and other factors, in addition to plasma levels of vitamin A, vitamin E, beta-carotene and lycopene.

One hundred and twenty-five participants were found to have carotid atherosclerosis as determined by carotid intima-media thickness of 0.8 millimeters or more. Body mass index, plasma hemoglobin, and high-density lipoprotein cholesterol were marginally higher among those diagnosed with atherosclerosis, and all of the nutrients measured were significantly reduced. Vitamin A, vitamin E, and lycopene levels were decreased by 50 percent or more among those with atherosclerosis compared with participants who

were not diagnosed with the condition, and beta-carotene levels were less than a third of those without atherosclerosis.

Oxidative stress resulting from the oxidation of low-density lipoprotein (LDL) cholesterol in the wall of the artery results in inflammation which stimulates the differentiation of immune system cells called monocytes into macrophages. Macrophages accumulate lipids to form foam cells which thicken the walls of the artery. Antioxidants such as those evaluated in the current study could help protect against this process by preventing LDL oxidation.

“Regular intake of foods rich in lycopene and other antioxidant vitamins may slow the progression of atherosclerotic processes and modify the early stages of atherosclerosis, with a consequent reduction in cardiovascular events,” the authors conclude.

## Oxidative stress profile (blood)

1. Malondialdehyde
2. Glutathione
3. CoEnzyme Q10
4. Vitamin C
5. b-Carotene (including cryptoxanthin and lycopene)

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